

Fig. 1

SEQ ID NO 1

-496 ACCATAGTC TCCATTATGCA TATTTTATAT CACTCTAACT TCTCTTGCGCC AAACTTGACCC TACTGTGCA ATTATTTTAC AITTCCTTGG CTCTGTGTTTC
 -396 ATTTATTTT AATTCCAGAA ACCACATCAA GTCTTTGCAG AATGAAGTAG AGCATAAGA AGTAGAGATG TACACACGCA TCTCTAAAAT CAGCCATGCC
 -296 TAGGCAAAGC AGCTTGCCT AAACACCCC ATACATTTT CATGATGTG TTGARGTGA GTAAACCTAAC CGGTTTTAT ATCCTCTAAA ATAAGGTGGA
 -196 TAGGAATGCT TTCAGCCCTT TCAATAGCT TGATTTCT TGTTTTGTT AGATCCCTCC TCTTGGTTG ATCATAGTAG TTACTGTATT TCTTTTATA
 -96 AGCTGGTCTG CAAAGGGTAG GGCTTGCGAGA CCATTCGAAA GTTGTGACGG CTGCTGACTA TATTCGCTGA GGTGGAACTC TGAAGCCAGA CTATCTATGT
 +5 GAAGGCACAA GCTCTGTTA TATAACACG AGTGAACGTCA GCATCAGTC GAAAAGTCT ATGTTTCCAG AAATACAGAT CCAAGACAAA GACAGG ATG
 rev TATA box M
 +104 GGC ACT GCT GGA AAA GTTACGGAAACATT intron 1 (5.6 kb) TTGCTTAATTCTTAG GTT ATT AAA TGC AAA GCA GCT GTG
 G T A G K ** 10
 L W E Q K Q P F S I E E I E V A P P K T K E V R I K **
 20 30
 CTT TGG GAG CAG AAG CAA CCC TTC TCC ATT GAG GAA ATA GAA GTT GCC CCA CCA AAG ACT AAA GAA GTT CGC ATT AAG GTA
 40 50
 ACGGTGAGGCTT intron 2 (1.0 kb) TGCTTTGAAACACAG ATT TTG GCC ACA CGA ATC TGT CGC ACA GAT GAC CAT GTG ATA
 ** I L A T G I C R T D D H V I
 60 70 80
 AAA GCA ACA ATG GTG TCC AAG TTT CCA GTG ATT GTG GGA CAT GAG GCA ACT GGG ATT GTA GAG AGC ATT GGA GAA GGA GTG
 K G T M V S K F P V I V G H E A T G I V E S I G E G V
 100 110
 ACT ACA GTG AAA CCA G GTATATGCAGGTGTC intron 3 (0.3 kb) ATTTTTTCTCTGTAG GT GAC AAA GTC ATC CCT CTC TTT
 T T V K P ** 90
 120 130
 CTG CCA CAA TGT AGA GAA TGC AAT GCT TGT CGC AAC CCA GAT GGC AAC CTT TGC ATT AGG AGC GA GTAGGTTTCAGTCAT
 L P Q C R E C N A C R H P D G N L C I R S D **
 140 150
 intron 4 (0.1 kb) TGATGTATCAAACAG T ATT ACT GGT CGT GGA GTA CTG CCT GAT GGC ACC ACC AGA TTT ACA TGC AAG GGC
 ** I T G R G V L A D G T T R F T C K K G
 170 180
 AAA CCA GTC CAC CAC TTC ATG AAC ACC AGT ACA TTT ACC GAG TAC ACA GTG GTG GAT GAA TCT TCT GTT GCT AAG ATT GAT
 K P V H H F M N T S T F T E Y T V V D E S S V A K I D
 190 200
 GAT GCA GCT CCT CCT GAG AAA GTC TGT TTA ATT GGC TGT GGG TTT TCC ACT GGA TAT GGC GCT GCT GTT AAA ACT GGC AAG
 D A A P P E K V C L I G C G F S T G Y G A A V K T G K
 170 180
 GAAAGAAACACGGTA intron 5 (7.1 kb) CATTTCTCTCACAG GTC AAA CCT GGT TCC ACT TGC GTC GTC TTT GGC CTG GCA
 ** V K P G S T C V V F G L G
 190 200
 GGA GTT GGC CTG TCA GTC ATC ATG GGC TGT AAG TCA GCT GGT GCA TCT AGG ATC ATT GGG ATT GAC CTC AAC AAA GAC AAA
 G V G L S V I M G C K S A G A S R I I G I D L N K D K
 210 220
 TTT GAG AAG GGC ATG GTC ATC GGT CCC ACT GAG TGT ATC AGT CCC AAG GAC TCT ACC AAA CCC ATC ACT GAG GTG CTG TCA
 F E K A M A V G A T E C I S P K D S T K P I S E V L S
 230 240 250
 GAA ATG ACA GGC AAC AAC GTG GGA TAC ACC TTT GAA GTT ATT GGG CAT CTT GAA ACC ATG GTAAAGCCCCAAAAAT intron 6
 E M T G N N V G Y T F E V I G H L E T H **
 260 270
 (1.4 kb) CCGTTTTAAACTCACT ATT GAT GCC CTG GCA TCC TGC CAC ATG AAC TAT GGG ACC AGC GTC GTG GTT GTC GGA CCT CCT
 ** I D A L A S C H M N Y G T S V V V G V P
 280 290
 CCA TCA CCC AAG ATG CTC ACC TAT GAC CCG ATG TTG CTC TTC ACT GGA CGC ACA TGG AAG GCA TGT GTC TTT GGA G GTCAG
 P S A K M L T Y D P M L L F T G R T W K G C V F G **
 300 310 320
 GAAAGCAAAG intron 7 (3.2 kb) TGCTCTTATTTCAG GT TTG AAA AGC AGA GAT GAT GTC CCA AAA CTA GTG ACT GAG TTC
 ** G L K S R D D V P K L V T E F
 330
 CTG CCA AAG AAA TTT GAC CTG GAC CAG TTG ATA ACT CAT GTT TTA CCA TTT AAA AAA ATC AGT GAA GGA TTT GAG CTG CTC
 L A K K F D L D Q L I T H V L P F K K I S E G F E L L
 340 350 360
 AAT TCA GGA CAA AG GTAACTGTCTTAT intron 8 (2.3 kb) CATTTCACATTTCAG C ATT CGA AGC GTC CTG ACG TTT TGA
 N S G Q S ** 370 374
 GATCCAAAGT GCGAGGAGGT CTGCTGAGTC ATGGGAACTT GCGCTTCTC TGTCTGACTT TCCG

Fig. 2

>gi|642473|gb|U16286|HSADHVII1 Human class IV alcohol dehydrogenase (ADH7) gene, exon 1

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ACCATAGTCA TCCATATTGA TATTTATAT CATCTCACT TCTCTTGCCTT AACTTGACC TACTGTTGCA ATTATTTAC ATTCCTTGG
CTCTGTTTC ATTTATTT AATTCAGAA ACCACATCAA GTCTTGCAG ATGAAGTAG AGCATTAAAGA AGTAGAGATG TACACACGCA
CTCTCTAAAT CAGCCATGCC TAGGCAAAGC AGCTTGCCT TAAACACCCA ATACATTTT CATGATTGTG TTGAAGTGAAG GTAACTAAC
CCGTTTTAT ATCCTTCAAATAAAGGTGGA TAGGAATGCT TTCAATAGCT TTGATTATCT TGTTTTGTT AGATCCCTCC
TCTGGTTTG ATCATAGTAG TTACTGTATT TCTTTTATA AGCTGGCTG CAAAGGGTAG GGCTTGCAGA CCATTGCAAA GTTGTACGG
CTGTGAGTCA TATTGCTGAA GGTGAACTC TGAAGCCAGA CTATCTATGT GAAGGCACAA GCTGCTGTTA TATACACAG AGTGAAGTGA
GCATCAGTCA GAAAAAGTCT ATGTTGCAG AAATACAGAT CCAAGACAA GACAGGATGG GCACTGCTGG AAAAGTAAGT GGAACATTC
TGCCCCCTCC TCATCATGAC CTAATGATGT GAGGCTGATA CTTAGAACTT TGAATGCTTAAAGAATTA AACACTTGGA GATATCCCTT
GAGGAATGAA ATGCTGGTG AGCAGGCTA CAGTGGGGAA AACACTGGAT ATGGTGTTC AGAGAATGTC AGTGGAAAGCA GGGGAAAGTT
GGAATAGTA TATCCAATG CAGCAAGGAA TTGGTGGAAA ATAGAGAAAT TGATTTATAT TGGCATTATT CATAATTGA TTCCGGATA
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AG

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>gi|642474|gb|U16287|HSADHVII2 Human class IV alcohol dehydrogenase (ADH7) gene, exon 2

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TAGGTGACCA TGGATCCATC ATTTAGTCAC TCTGGCTGC ATGTCATG CTTAACCAA AGGCACACAC AAGATGATT ATAAGGCTTA
TAATACTAGT GTTGTGATGAA ATCATCTG GAAAACCTAA AATATTATAT ATGCTCTTCT GTTCATATT ATACTAGTC GGGAGCTGTG
AAGTAAAGG CATAATTCA ACCCATTAA ATACTGCTT ATTCTTAGG TTATTAATG CAAAGCAGT GTGCTTGGG AGCAGAACG
ACCCCTCTCC ATTGAGGAAG TAGAAGTGC CCCACCAAAG ACTAAAGAAG TTGCAATTAA GGTAAGCGTG AGCCCTAGAG AACTTAAGCC
AAAAGCGTTA TCAAACCTAT ATTGAATATA GCACAGTGT GAGGCTGGAT TCTTAAATAA GGAGATGCTT CCCATGTTG GAGTATTAAT
TCCTTACTG GCTCTTATAT ATTGTTAAGG ATCTGGTGT ACTCGATGTC AAATTAATGA GTTCATTATC C

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>gi|642475|gb|U16288|HSADHVII3 Human class IV alcohol dehydrogenase (ADH7) gene, exon 3

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AACAAATTATA ATTTCTTCAA GAAGTTAAAT ATTCCTCCAA CAGTGAAATG ATCAGTTGT TGATTGGTC AATGTTTTG TCTTGAAACA
CAGATTTGG CCACAGGAAT CTGTCGACA GATGACCATG TGATAAAAGG AACAATGGT TCCAAGTTTC CAGTGTGTT GGGACATGAG
GCAACTGGGA TTGTAGAGAG CATTGGGAGA GGAGTGA CAGTGGAAAC AGGTATATGC AGGTGTCAAAC CCACAAGTTT GAAATAATTA
GGCTTGATT AGCCTATCAA AGGAAATAGC ACACACTAGG AATTATTAGA CGGATCC

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>gi|642476|gb|U16289|HSADHVII4 Human class IV alcohol dehydrogenase (ADH7) gene, exons 4-5

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CCTCAACCTT TAGAAGGCAA ACTTACGGTG TTATAAACCC TTAGAATATA TTTTAAAG TTTTACCTAT AGTATGGCT CAATTCACAT
TTGTTAATTT CATATTTAA CTTAAATGAA CAGCATCTTA TATCATGATT TTTTCTGT AGGTGACAA GTCATCCCTC TCTTCTGCG
ACAATGAGA GAATGCAATG CTGTCGCAAA CCCAGATGCC AACCTTGCA TTAGGAGCGA GTAGGTTCA GTCAATTAA CTTTATGTA
TTTACATTTT TCCTATGCTA ATTTTGAAAT TGAATTAATT AATACGTGA TTGATGTAT CAAACAGTAT TACTGGCTGT GGAGTACTGG
CTGATGCCAC CACCAAGATT ACATGCAAGG GCAAAACAGT CCACCACTTC ATGACACCA GTACATTAC TCGAGTACACA GTGCTGGATG
AATCTCTGT TGCTAAGATT GATGATGCACT CTCCCTGTA GAAAGTGTGT TTAATTGGCT GTGGGTTTC CACTGGATAT GGCCTGCTG
TAAAAACTGG CAAGGTAGA AACAGGGTAG GCTAGTT

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>gi|642477|gb|U16290|HSADHVII5 Human class IV alcohol dehydrogenase (ADH7) gene, exon 6

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GAGTTCACTC ATGATTTGTG TTTTAACTG GAGGCCCTTT TCAGGTTTCA CTTTTTGACC CTAACACCTA ACATGTTCAA GAACATTCCCT
CTCCACAGGT CAAACCTGGT TCCACTGCG TCGCTTTGG CCTGGGAGGA GTTGGCCTGT CAGTCATCAT GGGCTGTAAG TCAGCTGGTG
CATCTAGGAT CATTGGGATT GACCTCAACA AAGACAAATT TGAGAAGGCC ATGGCTGTAG GTGCCACTGA GTGTATCAGT CCCAAGGACT
CTACCAAAACC CATCAGTGAG GTGCTGTCAG AAATGACAGG CAACAAACCTG GGATACACCT TTGAAGTTAT TGGGCATCTT GAAACCATGG
TAAGACCCCA AAATTG

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>gi|642478|gb|U16291|HSADHVII6 Human class IV alcohol dehydrogenase (ADH7) gene, exon 7

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AACGATCTCC TCGTTTTAA ACTCAGATTG ATGCCCTGGC ATCCTGCCAC ATGAACTATG GGACCAGCGT GGGTTGAGGA GTTCCCTCCAT
CAGCCAAGAT GCTCACCTAT GACCCGATGT TCGCTCTTAC TGACGCGACA TGGAAAGGGAT GTGCTTTGG AGGTCAAGGAA AGCAAGGCCT
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TGATCT

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>gi|642479|gb|U16292|HSADHVII7 Human class IV alcohol dehydrogenase (ADH7) gene, exon 8

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AACACAGGGAA AAGTCATAGT GCAGGAAAGA GAAGGAATAA ATATAACATA ATAAAAGATA AGGATTATTT AGTAATGTC AAAGAGAAAAA
TGTGTGCTTA TTGCAAGGTG TGAAAAGCAG AGATGATGTC CCAAAACTAG TGACTGAGTT CCTGGCAAG AAATTGACC TGGACCGAGT
GATAACTCAT GTTTACCAT TTAAAAAAAT CAGTGAAGGA TTGAGCTGC TCAATTCAAGG ACAAAAGTAA CTGTTCTTA TGATGA

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>gi|642480|gb|U16293|HSADHVII8 Human class IV alcohol dehydrogenase (ADH7) gene, exon 9, and complete cds

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TTAAACTATC CTTCTTGAA AGATATGAAA ACAAGTCATT AAAACTCTC ATTTACATT TCAGCATTG AACGGCTCTG ACGTTTGAG
ATCCAAAGTG GCAGGAGGTC TGTGTGTC TGGTGAACG GACTTTCTCT TGTGAGAGTT CCC

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Fig. 3

Fragment number	Size	Contents	Forward and reverse primers
1	450bp	Promoter region, 5' UTR and first exon.	1-F AATCAGCCATGCCTAGGCAAA 1-R GGAGGGGACAGAAATGTTCCA
2	405bp	Second exon and parts of flanking introns	2-F GGCTGCATGTCTCATGCCTT 2-R CCAAACATGGGAAGCATCTCC
3	260bp	Third exon and parts of flanking introns	3-F CAGTTTGTGATTGGTGCAATGTT 3-R TGTGTGCTATTCCCTTGATAGGCT
4	510bp	Fourth and fifth exon and fourth intron and parts of flanking introns	4-F ATGGGCTCAATTCACATTGTT 4-R AACTAGCCTACCCTGTTCTT
5	340bp	Sixth exon and parts of flanking introns	5-F TTCAGGTTTCACTTTTGACCC 5-R CAAATTGGGTCTTAC
6	260bp	Seventh exon and parts of flanking introns	6-F ATCTCCTCCGTTAAACTC 6-R CTCATTCTTGGAAAGAAAGGCC
7	265bp	Eighth exon and parts of flanking introns	7-F ACAGGGAAAGTCATACTGCAGG 7-R TCATCATAAGAACAGTTAC
8	135bp	Nineth exon and parts of flanking introns	8-F TCCTTTCTTGAAAGATATGAA 8-R CTCCAGTTACCATGACAACAC

Fig. 4

Name	Frag- ment no.	Loca- tion	Wildtype sequence	Mutated sequence (mutations in bold are <u>underlined</u>)	Restriction enzyme (examples)	Type of mutation
M1	1	pro- moter	-102 to -88 TTTATAAGTTGGTCT	-102 to -88 TTTATAAG <u>C</u> TGGTCT	Alu I CviJ I	single nucleotide exchange
M2	1	5'- UTR	+20 to +32 TGTTATATACAAAC	+20 to +32 TGTT <u>A</u> CATACAAAC	Mae III	putative TATA-box disrupting
M3	2	second intron	in GDB U16287 nr. 415 to 426 AAATAAGGAGAT	in GDB U16287 nr. 415 to 426 AAATA <u>AGGG</u> GAGAT		2bp insertion
M4	3	second intron	in GDB U16288 nr. 81 to 95 TCTTGAAACACAGAT	in GDB U16288 nr. 81 to 95 TCT <u>TGAG</u> CACAGAT	BsiHKAI Bsp1286I	single nucleotide exchange
M5	3	third exon	in GDB U16288 nr. 205 to 218 GGAGAAGGAGTGAC	in GDB U16288 nr. 205 to 218 GGAGAAG <u>C</u> AGTGAC	(TspR I)	amino acid exchange Gly79Ala
M6	4	fourth intron	in GDB U16289 nr. 274 to 287 ACATTTTCCTATG	in GDB U16289 nr. 274 to 287 ACAT <u>TTG</u> CCTATG		single nucleotide exchange
M7	5	sixth exon	in GDB U16290 nr. 180 to 194 GCATCTAGGATCATT	in GDB U16290 nr. 180 to 194 GCAT <u>CTAG</u> AATCATT	Hinf I	silent mutation Arg218Arg

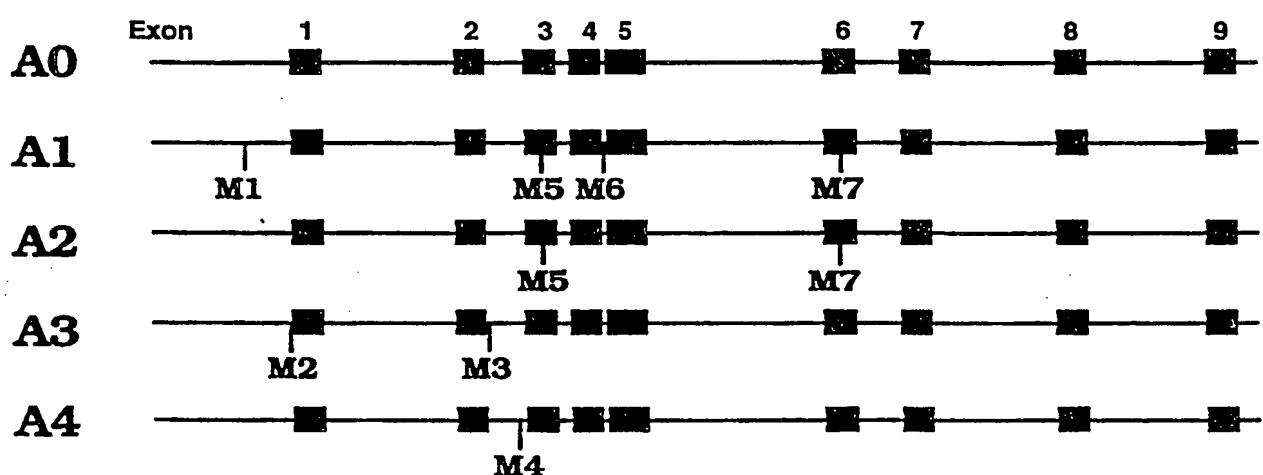
Fig. 5

Fig. 6A

	Allele frequency	Number of investigated alleles	Odds ratio	95%CI for the odds ratio	p value
Controls	4.62%	260	-	-	-
Non-familial cases	10.23%	88	2.354	0.9565 to 5.796	0.07
Familial cases	28.57%	28	8.267	3.028 to 22.565	0.0002
Patients total	14.66%	116	3.549	1.635 to 7.703	0.0014

Fig. 6B

Allele number	Allele frequency in controls (n=260)	Number of homozygotes in controls (n=130)	Number of homozygotes in PD patients (n=58)	P
A1	4.62%	0	2	<0.01
A3	11.15%	0	3	<0.05